WEST

Generate Collection Print

L9: Entry 3 of 6 File: USPT Nov 2, 1993

DOCUMENT-IDENTIFIER: US 5258149 A
TITLE: Process of making a membrane for high efficiency removal of low density lipoprotein-cholesterol from whole blood

Abstract Text (1):
The present invention relates to the efficient removal of low density lipoprotein cholesterol complex (LDL-C) from whole blood. More specifically, it relates to a process for making a microporous plasmapheresis membrane having an immobilized affinity agent. The immobilized affinity agent is polyacrylic acid bound directly and/or through an interaction with silica and/or calcium chloride to a microporous hollow fiber membrane.

Brief Summary Text (2):
The present invention relates to the efficient removal of low density lipoprotein cholesterol complex (LDL-C) from whole blood. More specifically, it relates to the use of an immobilized affinity agent on a microporous plasmapheresis membrane. The immobilized affinity agent is polyacrylic acid bound directly and/or through an interaction with amorphous silica and/or calcium chloride to a microporous hollow fiber membrane.

Brief Summary Text (14):
The present invention provides an improved process for preparing a membrane capable of removing low density lipoprotein cholesterol complex (LDL-C) directly from whole blood. An immobilized affinity agent is integral to the microporous plasmapheresis membrane. LDL-C removal is achieved during the plasmapheresis process in a single step. The immobilized affinity agent is polyacrylic acid bound directly and/or through an interaction with silica and/or calcium chloride to a microporous polysulfone hollow fiber membrane.

Brief Summary Text (15):
In one aspect, the process for immobilizing polyacrylic acid to the hollow fiber membrane is conducted at an acidic pH. Under acidic conditions undesirable side products, such as calcium carbonate, does not form as they do under basic conditions. The product formed by this process and its performance are superior to products manufactured under other conditions.

Brief Summary Text (16):
In another aspect, this process provides membranes wherein unincorporated silica is substantially removed from the final product. Silica acts as a pore former and viscosifier in membrane formation. However, once the initial membrane is formed, the presence of silica, especially silica not incorporated into the membrane network, is not necessary. Residual silica can be removed by treating the membrane under basic conditions.

Detailed Description Text (2):
A membrane has been discovered which has properties that are advantageous for the removal of the complex of low density lipoprotein and cholesterol (LDL-C) from whole blood or plasma. The polysulfone hollow fiber membrane has polyacrylic acid immobilized on its surface. The membrane has desirable mechanical and specificity characteristics for its intended purpose of LDL-C removal. The membrane can also be sterilized by autoclaving techniques.

Detailed Description Text (4):
The membranes of this invention are polysulfone-based polymeric compositions. Polysulfones are a known class of polymers which have been used to form various types

of membranes. Polysulfone membranes are of a substantially non-flexible physical form. "Polysulfone", "polyarylsulfone", "polyether sulfone", and "polyarylether sulfone" are each intended to define a polymeric material having a combination of sulfone groups, aryl groups, and ether groups in the polymer chain and which may also contain alkylene groups therein. Polysulfone (PS) polymers are available in a variety of grades with respect to molecular weight, additives, etc. High molecular weight polysulfones may be preferred for preparation of membranes with additional strength. UDEL.RTM. P-1700, and UDEL.RTM. 3500 polysulfone polymers (Amoco Performance Products Inc.) are suitable. Other suitable commercially available polysulfones are under the tradenames of ASTREL.RTM. (3M), VICTREX.RTM. (ICI), and RADEL.RTM. (Amoco). Polysulfone is used as the primary polymeric component of the membrane because of such beneficial characteristics as thermal stability, resistance to acid, alkali and salt solutions, high mechanical strength, etc.

Detailed Description Text (12):
At least about 8.0 wt. % and up to about 35.0 wt. % polysulfone in solvent should be used, preferably about 8.0 to about 22.0 wt. %. Above 35 wt. %, it will be difficult or impossible to dissolve the polysulfone in the solvent. Below about 8%, precipitation will be too slow for formation of hollow fibers, and the fibers are too fragile to handle practically. Up to about 20.0 wt. % of a second polymeric component, that is, one or more of the polymers or prepolymers described above, can be added to the PS solution.

Detailed Description Text (13):
The casting solution can also contain silica. Silica can be present in amounts of about 0.1to about 10% wt/wt, preferably about 5%. The silica does not dissolve in the casting solution, but rather forms a slurry. The silica aids in the immobilization of polyacrylic acid to the membrane during the next step of processing. Silica acts as a pore former and viscosifier to achieve a microporous structure with a nominal pore size of about 0.4 micron to about 0.65 micron. The casting solution can also contain polyacrylic acid (PAA). PAA can be present in amounts of about 0.01 to about 2% wt/wt, preferably about 0.5-1%.

Detailed Description Text (15):
The precipitation or coagulation mechanism of membrane formation is affected by the composition of the precipitation solution as well as that of the casting solution, and the composition of these two solutions are interdependent. In this disclosure, the terms "precipitation solution", "coagulation solution," "quench solution," and "quench bath" are used interchangeably to refer to the solution in which the membrane is formed. For formation of hollow fiber membranes, both an outer and a center precipitation or quench solution will be employed. The solvent content of the precipitation solution controls the rate at which the solvent comes out of the casting solution. In turn, this controls the rate of increase of the polymer concentration to the point at which the polymeric component precipitates out of the casting solution to form the membrane. The same solvent usually is used in the casting solution and the precipitation solution. 4-butyrolactone and blends of 4-butyrolactone and N-methylpyrrolidone are the preferred solvents. Other solvents are discussed above with regard to casting solutions.

Detailed Description Text (17):
In utilizing the method of this invention to prepare hollow fiber membranes, the precipitation solution used for the outer quench bath may be different from that used for the center quench fluid. In the preferred embodiment of this invention, the outer precipitation solution is water, and the center precipitation solution is 4-butyrolactone. Other solvents and non-solvents can be used as described above. In hollow fiber production, the center quench and outer quench are different phenomena. At center quench, a small volume of solution is used, which is almost in a static mode as compared with the casting solution. Conversely, the outer quench bath is present in large volumes and in a dynamic mode.

Detailed Description Text (18):
C. The Hollow Fiber Spinning Conditions

Detailed Description Text (19):
In preparing the hollow fiber membranes of this invention, a liquid-liquid or wet spinning process is used similar to that described in U.S. Pat. No. 4,970,030. That is, the casting solution is fed through an extrusion die (spinnerette) directly into a precipitation bath, while simultaneously introducing the center quench fluid through the central aperture of the spinnerette to mechanically maintain the hollow center hole

of the fiber. The fiber is fabricated and simultaneously quenched as it is drawn through the precipitation bath. By using this wet-spinning process, fibers with homogeneous pore structure and membrane morphology are produced.

Detailed Description Text (20):
One of the key factors in preparation of the hollow fiber membranes of this invention is use of the wet spinning process; that is, spinning the casting solution under water. In addition, selection of appropriate solutions for the inner and outer precipitation baths is important, as is the appropriate drawing or spinning rate of the fiber as it is formed. The presence of the center quench fluid also allows for simultaneous polymer precipitation from both the inner and outer surfaces of the fiber. The spinning rate is adjusted to allow for exchange of components between the casting and precipitation solutions. The solvent is leached out of the casting solution and is replaced by the non-solvent from the precipitation solution. As a consequence, polymer precipitation occurs, leading to formation of the membrane.

Detailed Description Text (22):
The precise spinning conditions are adjusted in order to yield hollow fibers meeting the desired physical requirements of inner diameter and wall thickness. Centering of the central aperture of the spinnette is required in order to achieve a fiber having a uniform wall thickness. Any spinnerette suitable for the preparation of hollow fiber membranes may be used to prepare the membranes of this invention, however, quartz or glass spinnerettes are preferred in order to achieve the small inside diameters required of the hollow fibers of the invention. The spinning conditions left to be adjusted are the flow rate and pressure of the casting solution and the flow rate and pressure of the center quench fluid. These adjustments are well within the knowledge and ability of one of ordinary skill in this art. The preferred temperature for the casting solution will be in the range of ambient temperatures, although higher temperatures, e.g., up to about 70.degree. C., may be employed to reduce the viscosity of the casting solution.

Detailed Description Text (23):
The dimensional and porosity characteristics of the membranes of this invention are such that LDL-C can pass through the fiber wall but most blood cells do not. Hemolysis occurs if numerous blood cells pass through the fibers, which is highly undesirable. However, passage of a small number of red blood cells through the fiber is acceptable. Generally speaking, membranes can be prepared which possess a pore diameter of between about 0.1 microns to about 0.7 microns, preferably between 0.4 and 0.65 microns. The inner diameter of the hollow fibers can range from about 150 to about 400 microns, preferably about 325 microns. The wall thickness can range from about ten to several hundred microns, preferably about 75 to about 100 microns.

Detailed Description Text (24):
D. Silica Removal

Detailed Description Text (25):
Membranes which have been prepared from a casting solution containing silica are optionally treated to remove residual silica. Silica which is not an integral part of the membrane network and is exposed to the bulk solution can be removed by treating the membrane in a strong basic solution. The basic solution can be any basic conditions, preferably 0.3N to 2.5N sodium hydroxide, most preferably 1.0N to about 2.0N sodium hydroxide. The membrane is generally treated with the basic solution for greater than 5 hours at room temperature. Fibers with silica are not microporous until the fibers are treated in the base to remove the bulk of the silica. The basic solution also aids in endotoxin removal. After this basic treatment, the membrane can optionally be treated with an acidic solution (i.e., approximately 0.1N HCl) to further aid in endotoxin removal prior to polyacrylic acid immobilization.

Detailed Description Text (27):
Polyacrylic acid (PAA) is a selective affinity agent for LDL-C. The presence of PAA on the surface of the PS hollow fiber membrane enables the effective removal of LDL-C from the plasma components of whole blood. Polyacrylic acid is immobilized on the surface of the fiber walls when the fibers are heated under pressure, preferably by autoclaving, for about 20 to about 40 minutes at about 122.degree. to about 130.degree. C. in an acidic PAA solution. In a preferred embodiment, the fibers are bathed in a PAA-containing solution and degassed under vacuum prior to the heat immobilization step. PAA is present in the PAA-containing solution in amounts of about 0.01 to about 3.0% wt/wt, preferably about 0.5-2.0%. The acidic conditions fall in the pH range of about pH 1.5 to about pH 5.5, usually about pH 2.85. This is a very simple and

inexpensive means for anchoring PAA onto the surface of porous membranes for use as an affinity agent to effectively bind LDL-C. The acidic conditions prevent the formation of undesirable side products such as calcium carbonate and silica-carbonate aggregates which can hinder the performance of the membrane. The membranes formed by this process have improved binding of LDL-C in the range of 10-12 mg LDL-C per ml of fiber wall volume.

Detailed Description Text (28):
Without wishing to be bound by any theory, it is believed that the vacuum degassing step followed by the autoclaving process allows all internal surfaces to be wet by the PAA solution. This enables the PAA to be immobilized on both the outer and inner surface of the PS hollow fiber membrane. The membrane is more effective at removing LDL-C when the vacuum degassing step is performed.

Detailed Description Text (29):
During the autoclaving step, PAA can be immobilized directly to the PS hollow fiber membrane or it can be immobilized indirectly through interactions with silica which may be embedded in the PS hollow fiber membrane. Greater amounts of PAA are immobilized to the membrane when silica is incorporated than without. While the actual nature of the interaction between PAA and silica is unknown, it is clear that addition of silica to the casting solution enhances the quantity of PAA bound to the membrane. This step also causes the fibers to be annealed and remain unaffected by subsequent autoclave steps.

Detailed Description Text (37):
The membranes are dried, preferably at room temperature in air containing less than 50% relative humidity to remove excess water. The fibers are then placed in a housing, and both ends of the fiber are potted in place in the housing. The preferred housing is a FOCUS.RTM. 70 fiber housing (National Medical Care, a division of W. R. Grace & Co.-Conn.) which is packed to about 42%-55% pacing density with about 1200-1600 fibers per housing. Any other convenient hollow fiber housings may be used.

Detailed Description Text (39):
The membranes and the device of this invention are excellently suited for removal of LDL-C from whole blood or plasma. FIG. 1 is a schematic representation of the mechanics involved in using the LDL-C removal device of the invention. Whole blood is removed from the patient, typically from a vascular access point in arm 10 using suitable blood removal apparatus 14. Some suitable apparati for blood removal include hypodermic needles, fistulas, subclavian catheters or other in-dwelling catheters. The blood passes from blood removal apparatus 14 into whole blood tubing 16 and is pumped via optional blood pump 18 into LDL-C removal device 28. As whole blood is pumped through the lumen of the hollow fiber membrane of LDL-C removal device 28, plasma is forced through the channels of the microporous fibers and separated from the cellular components of the blood. The plasma is treated in LDL-C removal device 28 exiting via plasma exit port 30. The remaining blood components (high hematocrit blood) passes down through the lumen of the membrane(s) and out exit port 34. The treated plasma is pumped via optional plasma pump 32 through plasma tubing 36 and is reunited with the high hemocrit blood at junction 44. The whole blood is then returned to the patient along with additional saline 38 added through saline tubing 40 at junction 46 as necessary via return tubing 42 to suitable blood return apparatus 12. The pressure is monitored by monitor 20 before blood enters LDL-C removal device 28, while blood is in LDL-C removal device 28 by monitor 24, and as blood exits LDL-C removal device 28 by monitor 22. Pressure can be adjusted as necessary using blood pump 18 and plasma pump 32.

Detailed Description Text (40):
Within the LDL-C removal device the action is as follows. The nominal pore size of the hollow fiber is such that it will reject or prevent the passage of blood cells through the membrane, yet permits the free passage of plasma and specifically the high molecular weight components such as LDL-C (2-6 million Daltons) through the membrane wall structure. As the plasma passes through the wall of the membrane, it comes into direct contact with the affinity agent PAA, and LDL-C is bound to the wall surface. The plasma which exits through the outer surface of the membrane contains less LDL-C. In a single step, the hollow fiber cartridge separates the plasma from the blood, removes the LDL-C from the plasma, and returns both plasma and blood components to the patients. Under normal operating condition for treatment of whole blood (flow rate (Q).sub.Plasma .ltoreq.0.35Q.sub.inlet and transmembrane pressure (TMP)<50 mm Hg), the cartridge is saturated with LDL-C in about 20-40 minutes. The operating conditions for plasma only can include significantly higher TMP since there is no concern for blood cell hemolysis. The cartridge can be substantially regenerated with a 1.0M salt wash with high speed flow in either direction, but optimally in the reverse direction of the

blood flow. This substantial regeneration represents about 85-95% of the original binding capacity restored.

Detailed Description Text (47):
Hollow Fiber Membrane Formation

Detailed Description Text (48):
A particular membrane of the invention having polyacrylic acid and silica bound to the polysulfone hollow fiber membrane is prepared as follows. Polysulfone, 210 g (UDELL.RTM. 1700, CAS #25135-51-7), was added to 1690 g of 4-butyrolactone (Kodak, CAS #96-48-0), in a glass jar with a sealable top containing a teflon (or other inert) liner. The mixture was rolled continuously on a roller mill for 48-72 hours at room temperature until the polymer was dissolved. To this solution of polysulfone in 4-butyrolactone was added 100 g of silica (SYLOX-2.RTM., Davison Division of W. R. Grace & Co.-Conn.). The jar was resealed and rolled continuously on the roller mill for at least 16 hours at room temperature to disperse the silica particles. This gave a casting solution that was 10.5 wt % in Polysulfone, 5 wt % in SYLOX-2.RTM. and 84.5 wt % in 4-butyrolactone.

Detailed Description Text (49):
The casting solution was then centrifuged at 2,000 rpm for 10 minutes to settle any poorly suspended silica particles. Next, the casting solution was pumped through a 40 micron stainless steel screen at 60 psi of pressure with dry nitrogen gas as the source of the driving pressure. After filtration the casting solution was de-gassed under mechanical vacuum at less than 10 mm Hg for at least 15 minutes and put in a stainless steel kettle that could be pressurized for delivery of casting suspensions to nozzle. No substantial solvent was lost during this degassing procedure due to the low volatility of the solvent. Under 60 psi of dry nitrogen gas, the casting solution was extruded through a glass nozzle within an orifice under the surface of a bath of deionized water. The core liquid of the spinnerette was 4-butyrolactone, driven by 80 psi dry nitrogen gas. The hollow fiber fabricated from the process during the under water spinning process was collected on a revolving wheel partially submerged under water. When the appropriate number of fibers were collected (800-1,200 revolutions), the fiber bundle was removed from the wheel, cut to chosen lengths, and soaked 16 hours at room temperature in deionized water.

Detailed Description Text (57):
A hollow fiber device as prepared in Example 2 containing 1200 fibers with a surface area of 1356 cm.sup.2 and total wall volume of 7.7 ml was perfused with plasma from a 100 ml reservoir of high cholesterol human plasma. The recirculation of high LDL-C plasma through the device was maintained at a flow rate of 58 ml/min giving a shear rate of 130 sec.sup.-1 to achieve a steady plasma filtration rate through the walls of the fibers. Plasma samples were taken from the plasma exit port and filtrated at time 0, 30 minutes, and 60 minutes. The average transmembrane pressure (TMP) remained constant throughout the run at 100 mmHg. Plasma filtrate flux values were 5.3 1/hr/m.sup.2 at 30 minutes and 4.9 1/hr/m.sup.2 at 60 minutes. Total cholesterol assays were performed on the plasma reservoirs using the Kodak EKTANCHEM.RTM. DT60 and nephelometry (Beckman Auto ICS Catalog Number 449310) to determine the level of the LDL-C associated protein apolipoprotein B.

CLAIMS:

1. A process for preparing a membrane which binds low density lipoprotein cholesterol comprising

(a) preparing a hollow fiber membrane from a casting solution comprising about 8 to about 22 weight % of a polysulfone polymer and 0 to about 10 weight % silica;

(b) submerging said hollow fiber membrane in an acidic solution comprising polyacrylic acid and 0 to about 30 weight % calcium chloride;

(c) immobilizing polyacrylic acid to said hollow fiber membrane by heating under pressure the submerged fibers of step (b); and

(d) annealing the hollow fiber membrane of step (c) by heating under pressure in water.

7. The process of claim 1 wherein said silica is present in amounts of about 0.1 to about 10 weight %.

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 6 of 6 returned.

☐ 1. Document ID: US 5558774 A

L9: Entry 1 of 6 File: USPT Sep 24, 1996

US-PAT-NO: 5558774
DOCUMENT-IDENTIFIER: US 5558774 A

TITLE: Aerated hot membrane bioreactor process for treating recalcitrant compounds

DATE-ISSUED: September 24, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tonelli; Fernando A.	Dundas			CA
Behmann; Henry	Puslinch			CA

US-CL-CURRENT: 210/612; 210/622, 210/626, 210/908

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 5496637 A

L9: Entry 2 of 6 File: USPT Mar 5, 1996

US-PAT-NO: 5496637
DOCUMENT-IDENTIFIER: US 5496637 A

TITLE: High efficiency removal of low density lipoprotein-cholesterol from whole blood

DATE-ISSUED: March 5, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Parham; Marc E.	Bedford	MA		
Duffy; Richard L.	Cambridge	MA		
Nicholson; Donald T.	Leominster	MA		

US-CL-CURRENT: 428/376; 210/500.23, 210/500.35, 210/500.41, 428/398

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 5258149 A

L9: Entry 3 of 6 File: USPT Nov 2, 1993

US-PAT-NO: 5258149
DOCUMENT-IDENTIFIER: US 5258149 A

TITLE: Process of making a membrane for high efficiency removal of low density lipoprotein-cholesterol from whole blood

DATE-ISSUED: November 2, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Parham; Marc E.	Bedford	MA		
Duffy; Richard L.	Cambridge	MA		
Nicholson; Donald T.	Leominster	MA		

US-CL-CURRENT: 264/41; 264/102, 264/184, 264/209.1, 264/211, 264/211.17, 264/233, 264/235

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

---

☐ 4. Document ID: US 5236644 A

L9: Entry 4 of 6 File: USPT Aug 17, 1993

US-PAT-NO: 5236644
DOCUMENT-IDENTIFIER: US 5236644 A

TITLE: Process of making membrane for removal of low density lipoprotein-cholesterol from whole blood

DATE-ISSUED: August 17, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Parham; Marc E.	Bedford	MA		
Duffy; Richard L.	Cambridge	MA		
Nicholson; Donald T.	Leominster	MA		

US-CL-CURRENT: 264/41; 264/102, 264/184, 264/209.1, 264/211, 264/211.17, 264/233, 264/235

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 5. Document ID: US 5136032 A

L9: Entry 5 of 6 File: USPT Aug 4, 1992

US-PAT-NO: 5136032
DOCUMENT-IDENTIFIER: US 5136032 A

TITLE: Method for separating phosphopolyol compounds using a separating agent

DATE-ISSUED: August 4, 1992

INVENTOR-INFORMATION: NAME	CITY	STATE	ZIP CODE	COUNTRY
Nagamatsu; Shinji	Hyogo			JP
Tanaka; Yoshikazu	Hyogo			JP
Shibata; Thoru	Hyogo			JP

US-CL-CURRENT: 536/18.7; 210/500.37, 210/500.38, 210/651, 210/654, 536/123, 536/4.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 6. Document ID: US 5084173 A

L9: Entry 6 of 6 File: USPT Jan 28, 1992

US-PAT-NO: 5084173
DOCUMENT-IDENTIFIER: US 5084173 A

TITLE: Hydrophilic composite porous membrane, a method of producing the plasma separator

DATE-ISSUED: January 28, 1992

INVENTOR-INFORMATION: NAME	CITY	STATE	ZIP CODE	COUNTRY
Nitadori; Yoshiaki	Oita			JP
Nakano; Toru	Nobeoka			JP
Hagihara; Takeaki	Oita			JP

US-CL-CURRENT: 210/321.89; 210/490, 210/500.36, 210/500.42, 427/245

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

Generate Collection | Print

Terms	Documents
l7 and silica	6

Display Format: CIT | Change Format

Previous Page Next Page